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SEQUENCE LISTING

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INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

<120> PEPTIDES SYNTHETIQUES OU NATURELS LIANT LA PROTEINE PHOSPHATASE 2A, METHODE D'IDENTIFICATION ET UTILISATIONS

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<151> 2001-07-27

<160> 44

<170> PatentIn version 3.1

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20 25

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amino acids with the same chemical function (such as Arg and Lys) are considered to be equivalent. The peptides to be analyzed for their binding with a PP2A or one of its subunits are generally selected from fragments of viral, parasitic or cellular proteins, which proteins have been shown to interact *in vivo* or *in vitro* with a type 2A protein phosphatase.

In particular, such viral parasitic or cellular proteins are selected from one of the following proteins: the t antigen of SV40 or polyoma, the middle t antigen of polyoma, the type B (B, B', B") subunit of PP2A, CK2α, CaMIV, p70S6-kinase, Pak1/Pak3, Tap42/alpha 4, PTPA, Set/I1/I2-PP2A, E4orf4, tau, *Vpr* or CD28, CCXR2 (chemokine receptor).

A preferred peptide of the invention is a fragment of the CD28 protein, and in particular peptides constituted by the sequences PRRPGPTRKHY (SEQ ID No: 33) and $(PRRPGPTRK)_2$ (SEQ ID No: 34), respectively corresponding to the peptides termed FD2 and FD3 the intracellular penetration capacity and effects on cell viability of which are described below in the experimental section. The present invention also pertains to peptide sequences that are distinguished from the preceding protein by substitution or deletion of amino acids, said distinct sequences nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

A particularly preferred peptide of the invention is a fragment of the *Vpr* protein of the HIV virus, in particular a fragment of the *Vpr* protein of the HIV-1 or HIV-2 virus, or a sequence that is distinguished from the preceding protein fragment by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits. The invention does not encompass the peptide, a fragment of the *Vpr* protein having the following sequence:

LFIHFRIGCQHSRIGITRRRRVRDGSSRP* (SEQ ID NO: 44) disclosed in the EMBL database, accession number P89821. In contrast, using said peptide in the context of the applications described below falls within the scope of the present invention.

Special examples of peptides derived from a protein which interacts with type 2A protein phosphatase derived from protamine that can be cited are the peptide with sequence RRRRRRRSRGRRRRTY (SEQ ID No: 41, termed FD8) or a sequence that is distinguished from SEQ ID No: 41 by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

Preferably again, a peptide of the invention is characterized in that it is included in one of the following sequences:

a) VEALIRILQQLLFIHFRI (SEQ ID No: 1);

b) RHSRIGIIQQRRTRNG (SEQ ID No: 2); or

c) a sequence that is distinguished from SEQ ID No: 1 or SEQ ID No: 2 by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

A particularly preferred peptide of the invention is a fragment of the peptide SEQ ID No: 2, said fragment consisting of or comprising the peptide with sequence RHSRIG (SEQ ID No: 36), termed FD9, the capacity for intracellular penetration and the effect on cell viability of which are described below in the experimental section.

The invention also concerns a compound with a polypeptide framework containing a peptide of the invention as defined above, said compound having a molecular weight in the range 10 to 150 Kdaltons and having the capacity to bind protein phosphatase 2A.

The invention also concerns a polypeptide, characterized in that it is constituted by a repeat of a peptide of the invention.

Particular examples of such polypeptides are the peptide RHSRIG polymers, and in particular the dimer $(RHSRIG)_2$ (SEQ ID No: 37) or the trimer $(RHSRIG)_3$ (SEQ ID No: 38), respectively termed FD10 and FD11, the capacity for intracellular penetration and the effect on cell viability of which are described below in the experimental section.

Peptides with sequences that are distinguished from SEQ ID No: 1 or SEQ ID No: 2 by substitution or deletion of amino acids and falling within the scope of the invention that can in particular be cited peptides the sequence of which is included in one of the sequences for the *Vpr* protein of different variants of type HIV-1, HIV-2 and SIV, corresponding to homologous sequences in variants of SEQ ID No: 1 or SEQ ID No: 2.

The following sequences can be cited: VEALIRILQQLL (SEQ ID No: 6), ALIRILQQLLFI (SEQ ID No: 7), IRILQQLLFIHF (SEQ ID No: 8), ILQQLLFIHFRI (SEQ ID No: 9), RHSRIGIIQQRR (SEQ ID No: 10), SRIGIIQQRRTR (SEQ ID No: 11) and IGIIQQRRTRNG (SEQ ID No: 12) corresponding to dodecapeptides identified as binding the subunit A of PP2A.

A particular sequence of the invention that is distinguished from SEQ ID No: 2 by deletion or substitution of amino acids is the sequence RHSRIGVTRQRRARNG (SEQ ID No: 40), also termed FD13 in the experimental section described below.

A preferred peptide of the invention is a peptide selected from sequences SEQ ID No: 1 and SEQ ID No: 2 and is characterized in that its administration induces apoptosis of tumour cells.

One method for selecting peptides that can induce tumour cell apoptosis can be implemented, for example, using the MTT viability test described in the experimental section.

A further preferred implementation of the invention provides a peptide characterized in that it derives from a fragment of the CK2α protein. In particular, the natural or synthetic peptide is characterized in that it derives from a fragment of the CK2α protein of the *Theileria parva* parasite.

More preferably, a peptide of the invention is characterized in that it is included in one of the following sequences:

a) RKIGRGKFSEVFEG (SEQ ID No: 3);

b) TVTKDCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 4);

c) KILRLIDWGLAEFYHP (SEQ ID No: 5);

d) a homologous sequence of SEQ ID No: 3, SEQ ID No: 4 or SEQ ID No: 5 derived from *P falciparum* or *Leishmania*; or

e) a sequence deriving from the sequences mentioned above by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to protein phosphatase 2A or one of its subunits, and in particular the sequence TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 43).

Among peptides that are distinguished from sequences SEQ ID No: 3, 4 or 5 that can be cited are sequences from site 1 (RKIGRGKFSEVFEG) (SEQ ID No: 3), in particular the peptide with the sequence RKIGRGKFSEVF and the peptide with sequence IGRGKFSEVFEG or sequences from site 2 (TVTKDKCVIKILKPVKKKKIKREIKILQNL) (SEQ ID No: 4), in particular the following peptides:

TVTKDKCVIKIL (SEQ ID No: 13);
TKDKCVIKILKP (SEQ ID No: 14);
DKCVIKILKPVK (SEQ ID No: 15);
CVIKILKPVKKK (SEQ ID No: 16);

IKILKPVKKKKI (SEQ ID No: 17);
ILKPVKKKKIKR (SEQ ID No: 18);
KPVKKKKIKREI (SEQ ID No: 19);
VKKKKIKREIKI (SEQ ID No: 20);
KKKIKREIKILQ (SEQ ID No: 21);
KIKREIKILQNL (SEQ ID No: 22);

and finally sequences from site 3 KILRLIDWGLAEFTHP (SEQ ID No: 5) or the peptide with sequence KILRLIDWGLAE (SEQ ID No: 23), the peptide with sequence LRLIDWGLAEFY (SEQ ID No: 24), or the peptide with sequence LIDWGLAEFYHP (SEQ ID No: 25).

One example of a peptide of the invention comprising a sequence homologous to T parva from site 3 of the CK2α protein in *P falciparum* is the peptide RQKRLI (SEQ ID No: 42). The invention also encompasses polymers of the peptide RQKRLI and in particular the trimer $(RQKRLI)_3$ (SEQ ID No: 35), termed FD7 in the experimental section.

Preferably, the invention pertains to a peptide derived from the CK2α protein of the parasite *Theileria parva*, characterized in that its administration reduces parasitic development.

A further embodiment of the peptides of the invention is characterized in that the peptides are derived from the tau protein. The tau sequence has a motif corresponding to the binding site for the E4orf4 adenovirus protein. In the case of Alzheimer's disease, the tau protein is regulated by protein phosphatase 2A. Such peptides should thus be useful in treating Alzheimer's disease.

The peptides identified by the method of the invention are particularly useful in treating certain tumours and certain viral or parasitic infections. The skilled person can select, using binding competition tests, novel peptides derived from the sequences identified using the method of the invention, said peptides competitively inhibiting binding of

**DESCRIPTION OF FIGURES**

**Figure 1**: Screening of a membrane containing peptides covering the sequence for *Vpr* of HIV-1 with the structural subunit A of PP2A (A) and the holoenzyme PP2A1 (B).

Covering the sequence of four peptides 54-57 defines the sequence of site 2 VEALIRILQQLLFIHFRI (SEQ ID No: 1)

Peptide 54: VEALIRILQQLL (SEQ ID No: 6)

Peptide 55: ALIRILQQLLFI (SEQ ID No: 7)

Peptide 56: IRILQQLLFIHF (SEQ ID No: 8)

Peptide 57: ILQQLLFIHFRI (SEQ ID No: 9)

Covering the sequence of three peptides 64 to 66 defines the sequence of site 1 RHSRIGIIQQRRTRNG (SEQ ID No: 2)

Peptide 64: RHSRIGIIQQRR (SEQ ID No: 10)

Peptide 65: SRIGIIQQRRTR (SEQ ID No: 11)

Peptide 66: IGIIQQRRTRNG (SEQ ID No: 12)

**Figure 2**: Screening of a membrane containing peptides covering the sequence for CK2α of *Theileria* with (A) the structural subunit A of PP2A and (B) the holoenzyme PP2A1.

Covering the sequence of two peptides defines the sequence of site 1 RKIGRGKFSEVFEG (SEQ ID No: 3)

Peptide 66: RKIGRGKFSEVF (SEQ ID No: 31)

Peptide 67: IGRGKFSEVFEG (SEQ ID No: 32)

Covering the sequence of ten peptides 74-83 defines the sequence of site 2 TVTKDKCVIKILKPVKKKKIKREIKILQNL (SEQ ID No: 4).

Peptide 74: TVTKDKCVIKIL (SEQ ID No: 13)

Peptide 75: TKDKCVIKILKP (SEQ ID No: 14)

Peptide 76: DKCVIKILKPVK (SEQ ID No: 15)

Peptide 77: CVIKILKPVKKK (SEQ ID No: 16)

Peptide 78: IKILKPVKKKKI (SEQ ID No: 17)

Peptide 79: ILKPVKKKKIKR (SEQ ID No: 18)

Peptide 80: KPVKKKKIKREI (SEQ ID No: 19)

Peptide 81: VKKKKIKREIKI (SEQ ID No: 20)

Peptide 82: KKKIKREIKILQ (SEQ ID No: 21)

Peptide 83: KIKREIKILQNL (SEQ ID No: 22)

Covering the sequence of three peptides defines the sequence of site 3 KILRLIDWGLAEFTHP (SEQ ID No: 5)

Peptide 129: KILRLIDWGLAE (SEQ ID No: 23)

Peptide 130: LRLIDWGLAEFY (SEQ ID No: 24)

Peptide 131: LIDWGLAEFYHP (SEQ ID No: 25)

**Figure 3**: Figure 3 is a histogram representing the intracellular penetration values obtained using a cell penetration test for the peptides cited in Table 3.

**Figure 4:** Figure 4 illustrates the effects of different peptides on the viability of Hela cells evaluated using a MTT viability test.

The viability of Hela cells (expressed as a percentage with respect to the initial population) was tested in the presence of increasing concentrations of peptides FD8 (4A), FD13/FD14 (4B) and FD11/FD12 (4C).

- FD11: a 18AA peptide corresponding to three repeats of a 6AA hexa motif derived from the sequence for FD14;
- FD14: FD14, which reproduces the binding site which we have characterized from HIV-1 *Vpr* with PP2A;
- FD13: This peptide corresponds to a HIV-1 *Vpr* sequence which is homologous with the FD14 peptide sequence, which represents a binding site with PP2A with another HIV-1 *Vpr*.

Further, viability studies carried out on the series of peptides shown in Table 1 allowed three peptides to be identified which inhibit the viability of Hela cells:

- FD8: affects the viability of Hela cells (Figure 4A);
- FD14: clearly affects the viability of Hela cells (Figure 4B);
- FD12: a 18AA peptide the sequence of which derives from that of the FD11 peptide (R is mutated into A). This peptide, which is homologous with the glucosamine transferase protein of *Chlamydia muridarum*, affects the viability of the Hela cell (Figure 4C). This biological effect could be due to an interaction with the plasma membrane.

**TABLE 3: Peptides mimicking binding sites for target proteins with PP2As**

| Original proteins | peptide codes | peptide sequences | SEQ ID No: |
|---|---|---|---|
| CD28 | | | |
| | FD2 | -PRRPGPTRKHY | SEQ ID No: 33 |
| | FD3 | -(PRRPGPTRK)2 | SEQ ID No: 34 |
| CK2α *T parva* | | | |
| | FD6 | -VKKKKIKREIKI | SEQ ID No: 20 |

| Original proteins | peptide codes | peptide sequences | SEQ ID No: |
|---|---|---|---|
| CK2α *P. Falciparum* (*T parva* analogue) | FD7 | -(RQKRLI)3 | SEQ ID No: 35 |
| *Vpr* (HIV-1) | FD9 | -RHSRIG | SEQ ID No: 36 |
| | FD10 | -( RHSRIG)2 | SEQ ID No: 37 |
| | FD11 | -( RHSRIG)3 | SEQ ID No: 38 |
| | FD12* | -(AHSRIG)3<br>(FD11 mutation, R...A) | SEQ ID No: 39 |
| | FD13 | RHSRIGVTRQRRARNG (FD14 analogue) | SEQ ID No: 40 |
| | FD14 | RHSRIGIIQQRRTRNG | SEQ ID No: 2 |
| Protamine | FD8 | RRRRRRRRSRGRRRRTY | SEQ ID No: 41 |

## DISCUSSION

Are peptides from certain proteins which interact with PP2As a novel anti-tumoral approach?

Our study has allowed to identify two penetrating peptides (FD8/FD14) derived from two proteins, *Vpr* and protamine, known to interact with PP2As. These peptides, which have in common sequences rich in arginine and lysine, could thus penetrate into the cell using a general internalization mechanism. Such a mechanism, which is common in internalizing peptides having arginine-rich sequences, has recently been proposed (Tomoki Suzuki et al, 2002, Possible existence of common interlization mechanisms among arginine-rich peptides, JBC 277, 2437-2443). In general, the presence of sequences that are rich in arginine or lysine characterize proteins binding PP2As, which suggests

## CLAIMS

1. A peptide less than 30 amino acids in size, preferably less than 20 amino acids, characterized in that *in vitro*, it specifically binds a type 2A protein phosphatase holoenzyme or one of its subunits.

2. A peptide according to claim 1, characterized in that it is a fragment of a viral, parasitic or cellular protein, said protein binding a type 2A protein phosphatase *in vitro*, or a sequence that is distinguished from the preceding protein fragment by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to the type 2A protein phosphatase or one of its subunits.

3. A peptide according to claim 2, characterized in that said viral, parasitic or cellular protein is selected from one of the following proteins: the t antigen of SV40 or polyoma, the middle t antigen of polyoma, the type B (B, B', B") subunit of PP2A, CXCR2 (chemokine receptor), CK2α, CaMIV, p70S6-kinase, Pak1/Pak3, Tap42/alpha 4, PTPA, Set/I1/I2-PP2A, E4orf4, tau, CD28 or *Vpr*.

4. A peptide according to claim 3, characterized in that it is a fragment of the CD28 protein selected from one of the following peptide sequences:

   a) PRRPGPTRKHY (SEQ ID No: 33); or

   b) a sequence distinguished from the sequence envisaged in a) by substitution or deletion of amino acids, said sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

5. A peptide according to claim 3, characterized in that said viral, parasitic or cellular protein is the *Vpr* protein of the HIV virus.

6. A peptide according to claim 5, characterized in that said *Vpr* protein is derived from the HIV-1 or HIV-2 virus.

7. A peptide according to claim 6, characterized in that it is selected from one of the following peptide sequences:

a) RRRRRRRSRGRRRRTY (SEQ ID No: 41); or

b) a sequence distinguished from the sequence envisaged in a) by substitution or deletion of amino acids, said sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

8. A peptide according to claim 6, characterized in that it is included in one of the following sequences:

a) VEALIRILQQLLFIHFRI (SEQ ID No: 1);

b) RHSRIGIIQQRRTRNG (SEQ ID No: 2); or

a sequence that is distinguished from SEQ ID No: 1 or SEQ ID No: 2 by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits.

9. A peptide according to claim 8, characterized in that it is the sequence RHSRIGVTRQRRARNG (SEQ ID No: 40).

10. A peptide according to claim 8, characterized in that it consists of the sequence RHSRIG (SEQ ID No: 36).

11. A peptide according to any one of claims 1 to 10, characterized in that its administration induces apoptosis of tumor cells.

12. A peptide according to claim 3, characterized in that said viral, parasitic or cellular protein is the CK2α protein.

13. A peptide according to claim 12, characterized in that said CK2α protein is derived from the *Theileria parva* parasite.

14. A peptide according to claim 12 or claim 13, characterized in that its administration reduces parasitic development.

15. A peptide according to any one of claims 12 to 14, characterized in that it is included in one of the following sequences:

a) RKIGRGKFSEVFEG (SEQ ID No: 3);

b) TVTKDCVIKILKFPVKKKKIKREIKILQNL (SEQ ID No: 4);

c) KILRLIDWGLAEFYHP (SEQ ID No: 5); or

d) a homologous sequence of SEQ ID No: 3, SEQ ID No: 4 or SEQ ID No: 5 derived from *P falciparum* or *leishmania*; or

a sequence deriving from the sequences mentioned above by substitution or deletion of amino acids, said distinct sequence nevertheless conserving the properties of binding to type 2A protein phosphatase or one of its subunits, and in particular the sequence TVTKDKCVIKILKPVKKKKIKREIKILQNL. (SEQ ID No: 43)

16. A peptide according to claim 15, characterized in that it is the peptide RQKRLI (SEQ ID No: 42).

17. A peptide according to one of claims 1 to 16, characterized in that it competitively inhibits interaction of the native protein from which it is derived with a PP2A holoenzyme or one of its subunits.

18. A peptide according one of claims 1 to 17, characterized in that it is coupled to a vector that is capable of transferring said peptide to a eukaryotic cell.

19. A polypeptide, characterized in that it is constituted by a repeat of a peptide according to any one of claims 1 to 13.

20. A polypeptide according to claim 19, characterized in that it is selected from one of the following sequences:

a) $(RHSRIG)_2$ (SEQ ID No: 37);

b) $(RHSRIG)_3$ (SEQ ID No: 38); or

c) $(RQKRLI)_3$ (SEQ ID No: 35).

21. A polynucleotide characterized in that its sequence consists of the sequence encoding a peptide according to any one of claims 1 to 20.

22. A polynucleotide, characterized in that its sequence is selected from one of the following sequences: SEQ ID No: 26, 27, 28, 29 or 30.

23. A polynucleotide, characterized in that it consists of a multimer of polynucleotide according to claim 21 or claim 22.

24. A cellular expression vector, characterized in that it comprises a polynucleotide according to one of claims 21 to 23 and regulatory sequences allowing expression of a peptide according to any one of claims 1 to 20 in a host cell.

25. A purified polyclonal or monoclonal antibody, characterized in that it is capable of specifically binding anyone of the peptides according to one of claims 1 to 20.

26. A pharmaceutical composition comprising a peptide according to one of claims 1 to 20, in combination with a pharmaceutically acceptable vehicle.

27. A pharmaceutical composition comprising an element selected from a polypeptide according to one of claims 21 to 23, an expression vector according to claim 24 or an antibody according to claim 25.

28. A peptide, characterized in that it is selected from one of the following sequences:

- SEQ ID No: 38;
- SEQ ID No: 40;
- SEQ ID No: 41.

29. A peptide, characterized in that it has sequence SEQ ID No: 20.

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